

## **REMARKS/ARGUMENTS**

### **I. Introduction**

Applicants acknowledge receipt of the Non-Final Office Action mailed July 1, 2004. Claims 36-87 are currently pending in the application. Claims 1-35 were canceled in the Preliminary Amendment filed August 3, 2001. Claims 77-85 have been allowed. Claims 36-76 stand rejected. Claims 49 and 50 have been canceled and incorporated into claim 36. Claims 36-48, 51-76, and 86-87 have been amended. No new matter has been added by these amendments.

### **II. The Examiner's Objections**

The Examiner has objected to claim 41 because Applicants have used the trade name Percoll and Ficoll without a trademark symbol. In response, Applicants have amended claim 41 to recite the trademark designation after the terms "Percoll" and "Ficoll".

### **III. The Examiner's Rejections**

#### **A. Rejections Under 35 USC § 112, second paragraph**

The Examiner has rejected claims 57, 86, and 87 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner has stated that the phrase "wherein said method further comprises forming an interphase enriched in the non-tumor cells having telomerase activity and the telomerase positive cells and depleted from telomerase positive non-tumor cells" in claim 57 is indefinite because it appears that part of the active method step is missing, and it is unclear what is depleted from the telomerase positive non-tumor cells. In response, Applicants have amended claim 36, from which claim 57 depends, to recite the

relevant active method steps. Applicants further point out that nothing is depleted from the telomerase positive non-tumor cells. Rather, telomerase-positive non-tumor cells are depleted from the interphase.

The Examiner has stated that claim 86 is indefinite and nonsensical because it recites "the flap opens into the lower compartment can opens from the outer edge." In response, Applicants have amended this claim to delete the phrase "can opens" in claim 86 in order to clarify the claim.

The Examiner has stated that claim 87 is indefinite because it depends on canceled claim 1. In response, Applicants have amended claim 87 to depend from amended claim 36. In light of these claim amendments, Applicants respectfully request that the Examiner withdraw the rejections of claims 57, 86, and 87 under 35 USC § 112.

**B. Rejections Under 35 USC § 102(e)**

The Examiner has rejected claims 36-47, 57-63, and 87 under 35 USC § 102(e) as being anticipated by Ts'o *et al.* (U.S. Patent No. 5,962,237) as evidenced by Wang *et al.* (U.S. patent application publication US 2002/0098535) and Soria *et al.*

The Examiner has stated that Ts'o *et al.* anticipates claims 36-47, 57-63, and 87 because Ts'o *et al.* allegedly disclose a method for the enrichment of cancer cells from a body fluid, comprising centrifuging the body fluid in a cell separation medium to separate the tumor cells from the blood having a density in the range of from about 1.06 g/ml to about 1.10 g/ml, wherein a first density gradient medium of 1.067 g/ml is preferred. Ts'o *et al.* also allegedly teach the use of Percoll™ or Ficoll™ for the cell separation medium and that the peripheral blood can be diluted with a diluting agent prior to placing it on a density gradient column. The Examiner has

alleged that although Ts'o *et al.* do not specifically disclose that the peripheral blood used in the centrifugation was treated with an anti-coagulant prior to loading on the density gradient column, it is standard in the art to add anti-coagulant substances to blood samples, such as those taught in Ts'o *et al.*, to prevent clotting. The Examiner has alleged that this fact has been further substantiated by Ts'o *et al.*'s use of plasma as a diluent for peripheral blood rather than serum.

Ts'o *et al.* also allegedly disclose examples of body fluids such as blood, urine, saliva, lymph, spinal fluid, semen, amniotic fluid, cavity fluids, and tissue extract, and that the rare cells are cancer cells from localized and non-localized cancer, including carcinomas of the brain, breast, bladder, colon, kidney, liver, lung, ovary, pancreas, prostate, rectum, and stomach, in addition to sarcomas, cancerous hematopoietic cells, melanomas, teratocarcinomas, neuroblastomas, and gliomas. Ts'o *et al.* also allegedly teach a method of forming an interface enriched in "lighter" tumor cells and "heavier" tumor cells using centrifugation at 300 x g to 600 x g or higher for 1-60 minutes, as well as the use of negative selection methods such as immunoadsorption to remove non-tumor cells from tumor cells. The Examiner has alleged that Ts'o *et al.* teach the isolation and *in vitro* culturing of rare (cancerous) cells and would thus fulfill the specific embodiments of claim 87.

The Examiner has alleged that Wang *et al.* teach that some of the tumor cells recovered from the density gradient separation of Ts'o *et al.* contain "stem-cell like cancer cells" which appear as undifferentiated stem cells. Thus, the Examiner has alleged that it would be inherent in the method of Ts'o *et al.* that non-tumor stem cells would be present in the interface with stem-cell like tumor cells and that the non-tumor stem cells would inherently be telomerase positive.

The Examiner has admitted that Ts'o *et al.* do not teach that the body fluid comprises non-tumor cells having telomerase activity and telomerase positive cells. However, the Examiner has alleged that it would be inherent in the interface of rare cells isolated by the method of Ts'o *et al.* that the cancer cells would be telomerase positive as evidenced by Soria *et al.* which teach that circulating epithelial cells in metastatic breast cancer are telomerase positive.

Applicants respectfully traverse this rejection. In order to reject a claim under 35 USC § 102, the Examiner must demonstrate that each and every claim element is contained in a single prior art reference. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986); *see also* MPEP § 2131 (August 2001). Claim terms are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (August 2001). Not only must the claim terms, as reasonably interpreted, be present, an allegedly anticipatory reference must enable the person of ordinary skill to practice the invention as claimed. Otherwise, the invention cannot be said to have been already within the public's possession, which is required for anticipation. *See Akzo, N.V. v. U.S.I.T.C.*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986); *In re Brown*, 141 USPQ 245, 249 (CCPA 1964).

If the Examiner relies on more than one reference to prove the inherency of a missing element in a reference cited as § 102 prior art, such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (This flexibility accommodates situations in which the common knowledge of technologists is not recorded in the reference, i.e.,

where technological facts are known to those in the field of the invention. 948 F.2d at 1268, 20 USPQ at 1749-50). *See also* MPEP § 2131.01. In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that an allegedly inherent characteristic necessarily flows from the teachings of the prior art. *Ex parte Levy*, 17 USPQ2d 1461 (BPAI 1990). In order for prior art to anticipate a claimed process, the inherency must be certain. *Glaxo, Inc. v. Novopharm Ltd.*, 830 F.Supp. 871 (EDNC 1993), 29 USPQ2d 1126, *aff'd.* (CAFC 1995), 52 F3d 1043, 34 USPQ2d 1565. The fact that a prior art reference may inherently have the characteristics of the claimed process is not sufficient. *Ex parte Skinner*, 2 USPQ2d 1788 (BPAI 1986). Inherency must be a necessary result and not merely a possible result. *In re Oelrich*, 666 F.2d 578, 212 USPQ 323 (CCPA 1981). That one skilled in the art might interpret a prior art reference as teaching a feature of the claimed invention required for anticipation is not sufficient. *Finnigan Corp. v. Int. Trade Com'n.*, 180 F.3d 1354, 51 USPQ2d 1001 (CAFC 1999).

Applicants submit that the prior art references Ts'o *et al.*, Wang *et al.*, and Soria *et al.* cited by the Examiner do not anticipate claim 36, as amended, because they do not teach every element of the amended claim. Claim 36, as amended, recites a "single-step" enrichment procedure for tumor cells that provides an important advantage over the teaching of Ts'o *et al.* because this single-step procedure makes it possible to enrich disseminated tumor cells of different types of tumor-like carcinoma cells from the colon, non-small cell lung cancer, mammary carcinoma, and prostate carcinoma cells. At the same time, this procedure significantly reduces unwanted blood cells which might interfere with further diagnostic steps and negates the need for further purification steps, such as those taught in Ts'o *et al.*

In contrast, Ts'o *et al.* teach a comparatively complicated two-step enrichment procedure, comprising a method of enriching cancer cells (i.e., prostate cancer cells) in a body fluid sample using a multiple-step density gradient centrifugation process, wherein the density gradient separations are carried out at least twice (col. 6, lines 19-25, col. 10, lines 1-4). The centrifugation process of Ts'o *et al.* may result in four to six different regions including a plasma, interface, gradient, and cell pellet which comprises a first fluid. The gradient and interface are then subsequently combined to produce more collection fluids.

Ts'o *et al.* differ from the present invention because they do not teach the simultaneous enriching of tumor cells and depleting of unwanted blood cells from a body fluid. Nor do they teach a centrifugation vessel that is separated by a porous barrier, a filter, a sieve, or a flap into an upper compartment and a lower compartment, wherein the body fluid is in the upper compartment and the cell separation medium is in the lower compartment, as in claim 36.

Ts'o *et al.* also differ from the claimed invention because they teach that "the gradient medium should have a density of no less than about 1.06 g/mL, more preferably no less than about 1.068 g/mL" (col. 5, line 65), whereas claim 36 of the present invention recites a cell separation medium in the range from about 1.055 to 1.065 g/mL, which lower limit is below 1.06 g/mL. Thus, Applicants submit that because Ts'o *et al.* do not anticipate all of the limitations of amended claim 36, from which claims 37-48 and 51-63 depend, Ts'o *et al.* should not be considered prior art under 35 U.S.C. § 102(e).

Applicants further submit that Wang *et al.* should not be considered prior art under 35 USC § 102(e) because as mentioned below, Applicants' earliest priority date of February 3, 1999 (German patent DE 199 04 267 A1) is before Wang *et al.*'s earliest priority date of February 10,

1999. Therefore, Applicants respectfully submit that in view of the English translation of German patent DE 199 04 267 A1 provided herewith, Wang *et al.* should no longer be considered prior art.

Although Soria *et al.* teach that all cancer cells exhibit telomerase activity and that telomerase activity in harvested epithelial cells can be used to detect circulating epithelial cancer cells in patients with metastatic breast cancer, Applicants note that the circulating epithelial cells taught by Soria *et al.* would not necessarily be comparable to the prostate cancer cells of Ts'o *et al.* because each type of cancer cell is different, with its own unique etiology and its own specific set of antigens. Although Ts'o *et al.* do teach other types of cancer cells, Ts'o *et al.* primarily focuses on prostate cancer cells. Ts'o *et al.* teach that very few prostate cancer cells are actually found circulating in the bloodstream of cancer patients (i.e., 2 in  $10^7$  leukocytes, for example) (col. 1, lines 42-48). Thus, telomerase activity of the prostate cancer cells of Ts'o *et al.* would not be as easily detected, compared to the metastatic breast cancer epithelial cells taught in Soria *et al.* Furthermore, even if after isolation, the rare (cancerous) cells at the resulting interface taught by Ts'o *et al.* would be telomerase-positive, Applicants submit that because Ts'o *et al.* should no longer be considered prior art under 35 USC § 102(e) over amended claim 36 for the reasons mentioned above, the inherency of Soria *et al.* in view of Ts'o *et al.* should be considered moot. Thus, Applicants respectfully request that the rejections under 35 USC § 102(e) of claims 37-47, 57-63, and 87, which depend from amended claim 36, should be withdrawn.

**C. Rejections Under 35 USC § 103(a)**

**1. Ts'o *et al.***

The Examiner has rejected claims 36-53, 55, and 57-74 under 35 USC § 103(a) as being unpatentable over Ts'o *et al.* for the same reasons set forth under 35 USC § 102(e) above. In

addition, the Examiner has alleged that Ts'o *et al.* teach a kit for the enrichment of cancer cells from blood comprising a density gradient medium of at least about 1.067 g/ml. The Examiner has alleged that Ts'o *et al.* do not teach a kit comprising a density gradient medium of less than 1.067 g/ml or that the centrifugation vessel is cooled prior to removal of the interface comprising the tumor cells. However, the Examiner has alleged that Ts'o *et al.* teach that the density gradient medium may range from 1.06 to 1.10 g/ml, and that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to make a kit having a gradient medium ranging from 1.06 to 1.10 g/ml, based on the range of density gradients appropriate for the separation of cancer cells from peripheral blood taught by Ts'o *et al.*

The Examiner has alleged that it would have been obvious to provide a centrifugation vessel comprising a porous piece of plastic or a sieve so that the body fluid can be quickly loaded into the centrifugation vessel and retained before subjecting it to centrifugation and that one of ordinary skill in the art would have been motivated to make such an alteration in the centrifugation vessel in order to process multiple samples because having a porous plastic barrier would prohibit the mixing of the body fluid sample with the cell separation medium until the tubes were subjected to centrifugal force. Thus, the Examiner has alleged that multiple samples could be loaded with the body fluid sample and placed in the centrifuge at one time without allowance for variability in mixing with the cell separation medium that would occur as an experimental variable without the porous barrier separating the upper and lower compartments.

The Examiner has also alleged that the presence of a plastic support for a porous barrier or a plastic porous barrier of the same substance as the centrifugation vessel would fulfill the specific embodiment of claim 55 drawn to a hydrophobic material and that the dimensions of the plastic support for a porous barrier or a plastic porous barrier would be similar to the thickness of

the centrifugation vessel itself and would thus render obvious claims 52 and 55 drawn to specific thicknesses.

The Examiner has further alleged that it would have been obvious to cool the density gradient prior to the removal of the interface comprising the tumor cells, as in claim 48 of the present invention, because one of ordinary skill in the art would know that this is a standard procedure in the biological arts that is used to slow down or halt enzymic reactions within the cells in the interface which could lead to cell death and apoptosis. The Examiner has alleged that one of ordinary skill in the art would be motivated to isolate the intact circulating cancer cells for diagnostic purposes and that allegedly the death of the cancer cells during the gradient separation would not lead to a representative sample of circulating cancer cells.

Applicants respectfully traverse these rejections. MPEP § 2142 sets forth three requirements that must be met in order to establish a *prima facie* case of obviousness under § 103. First, there must be some suggestion or motivation, either in the reference, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success of producing the claimed invention upon modifying the reference. Finally, the prior art reference must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). See MPEP § 2142. The initial burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the reference must expressly or impliedly suggest the claimed invention, or the Examiner must present a convincing line of reasoning as to

why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

Applicants respectfully submit that the Examiner's allegations of obviousness fail to rise to the standard required under MPEP § 2142, and therefore the rejection is improper and should be withdrawn. Applicants also respectfully submit that the Examiner has failed to meet the burden of proving that one of ordinary skill in the art would have been motivated to successfully produce the claimed invention by modifying the method of enriching cancer cells taught by Ts'o *et al.*

Claims 49 and 50 have been canceled, so the rejection of these claims under 35 USC § 103(a) is moot. Applicants submit that claims 36-48, 51-53, 55, and 57-63 should no longer be rejected over Ts'o *et al.* for the same reasons mentioned above under 35 USC § 102(e).

Claims 64-75 pertain to a kit comprising a cell separation medium which has a density in the range from 1.055 to 1.065 g/ml. The kit taught by Ts'o *et al.* comprises "at least first and second gradient density media, wherein the first gradient density medium has a density of at least about 1.067 g/mL, and the second gradient density medium has a density of at least about 1.077 g/mL . . . ." (col. 12, lines 31-36). Therefore, the medium in the kit taught by Ts'o *et al.* is outside the range of 1.055 to 1.065 g/ml recited in claim 64.

Applicants further submit that Ts'o *et al.* would not have motivated one of ordinary skill in the art to experiment with different mediums within the range of 1.06 to 1.10 g/ml to produce the kit of claim 64. Ts'o *et al.* teach that the range of 1.06 to 1.10 g/ml pertains specifically to methods involving enriching prostate cancer cells from blood using a double density gradient (col. 9, line 62-col. 10, line 4), whereas the claimed invention does not teach a double density gradient, and the claimed tumor cells of the kit are not specific to prostate cancer cells.

Applicants submit that even if one of ordinary skill in the art were to experiment within the range of 1.06-1.10 g/mL for prostate cancer cells or other types of cancer cells, one of ordinary skill in the art would ultimately arrive at the optimal density gradient of 1.068 g/mL taught in Ts'o *et al.* (col. 10, lines 5-13), which is still outside the claimed range of 1.055 to 1.065 g/ml.

**2. Ts'o *et al.* in view of Wang *et al.***

The Examiner has rejected claims 36-53, 55, and 57-74 under 35 USC § 103(a) as being unpatentable over Ts'o *et al.* for the reasons set forth above under 35 U.S.C. § 102(e), and claims 54 and 75, further in view of Wang *et al.* The Examiner has alleged that Ts'o *et al.* render obvious the specific embodiments of claims 36-53, 55, and 57-74.

The Examiner has stated that Ts'o *et al.*, as evidenced by Wang *et al.* do not teach or render obvious a porous barrier, filter, or sieve having a pore size of 20-30 mm, but that Wang *et al.* allegedly teach circulating cancer cells which are "stem-like" cancer cells having a diameter of about 12-20 mm in contrast to circulating cancer cells which are dying cancer cells having a diameter of about 30-50 mm. The Examiner has alleged that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a porous barrier, filter, or sieve having a pore size of 20-30 mm in order to eliminate the terminal cancer cells from the tumor cell interface. The Examiner has alleged that one of ordinary skill in the art would have been motivated to use a porous barrier, filter, or sieve with such pore size based on the teachings of Wang *et al.* regarding the sizes of circulating terminal cancer cells versus circulating stem-cell like cancer cells because allegedly one of ordinary skill in the art would have known that the non-terminal stem-cell like cancer cells represent potential metastasis of a primary cancer, whereas circulating terminal cancer cells would not result in viable metastatic foci within a patient. The Examiner has alleged that the Applicant may not rely upon the foreign

priority documents to overcome this rejection because a translation of said documents has not been made of record in accordance with 37 CFR § 1.55.

In response, Applicants note that claims 49 and 50 (from which claim 54 depends) have been canceled, so the rejection of claims 49-50 and 54 should be moot. As mentioned above, Applicants include herewith an English translation of the foreign priority document DE 199 04 267 A1, from which the instant invention claims priority. The priority date of the German patent DE 199 04 267 A1 is February 3, 1999, which pre-dates the February 10, 1999 priority date of Wang *et al.* Applicants respectfully submit that in view of the English translation of priority document DE 199 04 267 A1 provided herewith, Wang *et al.* should no longer be considered prior art. Thus, Applicants submit that the rejection of claims 36-48, 51-53, 55, and 57-74 in view of T'so *et al.* and claim 75, further in view of Wang *et al.*, should be rendered moot for the reasons mentioned above under § 102(e) and in view of the provision of the English translation of the German patent DE 199 04 267 A1 provided herewith.

**3. Ts'o *et al.* in view of Wang *et al.*, Soria *et al.*, and the Pharmacia Biotech Catalog**

The Examiner has rejected claims 36-47, 57-63, and 87 under 35 U.S.C. § 103(a) as being unpatentable over Ts'o *et al.* as evidenced by Wang *et al.* and Soria *et al.*, in view of a Pharmacia Biotech Catalog product description of density marker beads. The Examiner has alleged that the teachings of Ts'o *et al.*, Wang *et al.*, and Soria *et al.* anticipate the specific embodiments of claims 36-47, 57-63, and 87, and that while neither Ts'o *et al.*, Wang *et al.*, or Soria *et al.* teach the use of dye to allow for the localization of an interphase enriched in tumor cells, the Pharmacia Biotech catalog teaches the use of color density marker beads within a cell separation medium, such as Percoll, to allow for a determination of the densities of cells

separated on a cell separation medium. The Examiner has alleged that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of the colored density marker beads as taught by the Pharmacia catalog because of the ease of identifying a particular density using the colored beads included in the cell separation medium.

Applicants respectfully traverse this rejection. Applicants submit that the rejections under 35 USC § 103(a) of claims 37-47, 57-63, and 87, which depend from amended claim 36, should be withdrawn for the reasons mentioned above under 35 USC § 102(e). Applicants further submit that the rejection of these claims in view of Wang *et al.* should be withdrawn in view of the Applicants' provision of the English translation of German patent DE 199 04 267 A1, mentioned above. Applicants also submit that even if Soria *et al.* were to be considered prior art, it would not necessarily be obvious to one of ordinary skill in the art to combine Soria *et al.* with Ts'o *et al.* to produce the claimed invention because while Soria *et al.* teach that telomerase is a hallmark of cancer, is absent from normal epithelial cells, and can be used as a molecular marker for the detection of cancer cells, Applicants point out that in peripheral blood, an elevated telomerase activity is shown not only by tumor cells but also by hematopoietic stem cells and activated lymphocytes (page 2, paragraph 3 (lines 12-19) of the specification). Thus, the determination of telomerase activity in cancer cells, as taught by Soria *et al.* may be due to factors other than or in addition to the presence of cancer cells. Hence, the desirability in the claimed invention of separating telomerase-active hematopoietic stem cells and lymphocytes from tumor cells. Applicants submit that Soria *et al.* and the Pharmacia biotech catalog references should not be considered prior art, and the rejections under 35 USC § 103(a) should be withdrawn.

**IV. Conclusion**

In view of the above amendments and remarks, it is respectfully submitted that claims 36-48, 51-76, and 86-87, as amended, are in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

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